

# Botanical Medicines Used for Kidney Disease in the United States

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Herbal medicines are being used with greater frequency by practitioners of natural medicine in the United States. Many categories of herbs are used, primarily angiotensin antagonists, nonspecific nephroprotective, and immunomodulating/adaptogenic herbs. The most common herbs in each category are discussed both from a historical and scientific perspective. For the first time, a case series of the use of the proposed herbal angiotensin antagonist herb indigenous to the United States, *Lespedeza capitata*, is reported based on the author's clinical practice.

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## INTRODUCTION

Botanical medicine (phytomedicine) has a long history in the United States, starting well before the European conquest. Numerous reports document the historical use of medicinal plants, fungi, and algae by native peoples of North America, much of which continues today despite the massive disruption of their cultures.<sup>1-3</sup> The United States is often referred to as a melting pot as people from all over the world have migrated there to settle, and they have brought their local herbs with them, resulting in a diverse and complex pattern of use. This review will focus on herbs that originate from North America, Eurasia, and Central/South America used in the United States for patients with chronic kidney disease (CKD).

Since 1994, herbal medicines have been regulated as dietary supplements in the United States due passage of a law known as the Dietary Supplements Health and Education Act.<sup>4</sup> This separates and distinguishes them from foods or drugs. Prior to this law, most herbs were seen as foods. If claims are made as to the efficacy of herbs for particular diseases, or for prevention of the same, they are regulated as drugs. The complicated and evolving regulatory framework for herbs in the United States has both contributed to ongoing popularity of herbs by improving their purity, but also altered

the industry as companies attempt to comply with mounting regulations.

Chronic kidney disease and end-stage renal disease are common in the United States. The prevalence of CKD stages 1 to 4 is estimated to be 131 000 per million people (13.1%) in the United States for the period of 1999 to 2004, which rose from 10% in the period of 1988 to 1994, largely attributable to the rise in diabetes mellitus and hypertension.<sup>5</sup> According to the United States Renal Data System, the prevalence of an estimated glomerular filtration rate less than 60 mL/min/1.73 m<sup>2</sup> was 6.9% to 7.8% (depending on the estimating equation used), and the prevalence of a urine albumin-creatinine ratio greater than 30 was 9.9% for the period of 2001 to 2008.<sup>6</sup> The prevalence of end-stage renal disease is estimated to be 1738 per million people in the United States; this rate is 5284 in African-Americans and 2735 in Native Americans.<sup>7</sup> These lead to enormous utilization of dialysis and kidney transplantation, both of which incur enormous direct and indirect costs, most of which is paid for by the government medical program Medicare.<sup>8</sup> Though there is little published literature, it appears that use of herbal medicine is fairly common among patients with CKD and on dialysis in the United States.<sup>9</sup> Though herbal medicines are sometimes portrayed in the medical

literature as potentially dangerous in CKD patients and those on dialysis if used properly, they actually have significant potential to prevent development and progression of CKD and to make dialysis more tolerable and effective. Evidence supporting this contention will be reviewed here, along with details on how these herbs are currently used clinically.

### HERBAL ANGIOTENSIN ANTAGONISTS

Some herbs appear, at least in part, to act as angiotensin converting enzyme (ACE) inhibitors and thus help preserve renal function (Table 1).

*Lespedeza capitata* (round-headed lespedeza) is a shrub native to the eastern portion of North America. The flowering tops are used as medicine. Research conducted on multiple species in the genus repeatedly confirms high content of flavonoids and related polyphenolic compounds.<sup>10,11</sup> Proanthocyanidins from *L capitata* have been shown to inhibit ACE in vitro.<sup>12</sup>

Several older, poor-quality European clinical research trials found that injecting a purified flavonoid and proanthocyanidin extract from *L capitata* had salutary effects in people with chronic renal failure.<sup>13-16</sup> A tincture was also used orally in some reports.<sup>17</sup> Details of the exact preparations used and their doses could not be obtained.

In the United States, *L capitata* tincture (made with 30% to 50% ethanol) is generally the form used. The typical dose is 2 mL to 5 mL 3 times per day depending on the size of the patient.<sup>18</sup> In formulas

it is often used in lower amounts, depending on synergy of the other herbs to work with it. Table 2 provides a listing of patients seen by the author in practice over an eight year period with kidney disease treated with *L capitata* tincture as part of a complex, individualized herbal formula in each case. In every case other treatments (supplements and diet generally; some patients were already on various pharmaceuticals) were used, but *L capitata* was one consistent factor between patients. Clearly these cases cannot establish the efficacy of *L capitata* but they provide some preliminary evidence that at least in some patients, combined with other treatments, it may be of value and should be further investigated. Also there was no clear adverse effect from *L capitata* in these patients with the exception of 1 patient who had persistent nausea (though other herbs in her formula may have been at fault).

*L virgata* (wand lespedeza) and *L cuneata* (ye guan men) herb are used in Chinese herbal medicine for CKD. In one animal model of minimal change nephropathy, an unknown extract of *L virgata* decreased various signs of kidney damage due to doxorubicin injection.<sup>19</sup> This provides interesting support that the entire genus might be helpful for kidney disease, and should be further investigated.

*Crataegus spp* (hawthorn) leaf, flower, and fruit all contains proanthocyanidins that have ACE inhibiting properties.<sup>20,21</sup> The chemistry and actions of this plant are thus very similar to that of *Lespedeza*, raising the prospect of *Crataegus* as a beneficial plant in CKD. This has not been directly tested. *Crataegus* extracts have been shown to have a tendency to lower blood pressure in patients with hypertension but not CKD in double-blinded research.<sup>22</sup>

*Ganoderma lucidum* (reishi, ling zhi) is a fungus that grows on rotting wood and produces a hard, rich brown-black fruiting body. Like many medicinal mushrooms, it contains complex polysaccharides with immunomodulating effects that may be relevant to patients with CKD due to autoimmune diseases and to correct immunodeficiency related to renal failure.<sup>23</sup> However, it also contains bitter-tasting triterpenoids (largely absent from the mycelium of this fungus and from other species in the genus).<sup>24</sup> Reishi's triterpenoids have ACE inhibiting activity.<sup>25</sup> *Ganoderma* has demonstrated nephroprotective activity in several animal

**Table 1.** Major Herbs Used in the United States

#### Angiotensin-Converting Enzyme Inhibiting Herbs

- Allium sativum* (garlic) bulb, Liliaceae
- Crataegus spp* (hawthorn) herb, Rosaceae
- Ganoderma lucidum* (reishi) fruiting body, Polyporaceae
- Lespedeza capitata* (round-headed lespedeza) herb, Fabaceae
- Salvia miltiorrhiza* (Chinese sage, *dan shen*) root, Lamiaceae

#### Nephroprotective Herbs

- Parietaria judaica* (pellitory-of-the-wall) herb, Urticaceae
- Rheum palmatum* (rhubarb, *da huang*) root, Polygonaceae
- Silybum marianum* (milk thistle) seed and silymarin extract, Asteraceae
- Urtica dioica* (stinging nettle) seed, Urticaceae

#### Immunomodulating/Adaptogenic Herbs

- Astragalus membranaceus* (astragalus, *huang qi*) root
- Cordyceps spp* (cordyceps, *dong chong xiao cao*) mycelium
- Codonopsis spp* (codonopsis, *dang shen*) root
- Glycyrrhiza glabra* (licorice) and *G. uralensis* (*gan cao*) root

**Table 2.** Cases of Use of *Lespedeza capitata* in the Author's Practice

Patient	Gender	Year of birth	Diagnosis	Daily Tincture Dose, mL	Duration of Use, mo	Outcome	Treatment Benefit
1	Female	1949	Diabetic nephropathy	3	36	Stable serum creatinine, no dialysis	Yes/Likely
2	Male	1956	Hypertensive nephropathy	5 to 7.5	2	Slowed rise in serum creatinine, patient asymptomatic	Yes/Likely
3	Female	1968	Idiopathic, asymptomatic unilateral nonactive kidney	3	3	Mildly reduced serum creatinine	Yes/Likely
4	Male	1927	Hypertensive nephropathy	2.25	2	serum creatinine stable	Yes/Likely
5	Male	1941	Status post traumatic nephrectomy; glomerulonephritis	3 to 7.5	5	serum creatinine fell, edema improved, blood pressure lowered	Yes/Likely
6	Male	1952	Status postnephrectomy for RCC stage I	3	12	Stable serum creatinine and blood pressure	Yes/Likely
7	Male	1948	Post-TURB rise in serum creatinine	2.25	0.5	serum creatinine normalized	Yes/Likely
8	Female	1970	IgA nephropathy	2.25 to 3	48	serum creatinine steadily climbed, avoided dialysis for 2 years but ultimately went on it	Yes/Likely
9	Male	1951	IgA nephropathy with acute renal failure	1.5	2	serum creatinine normalized, residual proteinuria still present	Yes/Likely
10	Male	1959	IgA nephropathy	2.25 to 1	24	Stable proteinuria, stable serum creatinine, stable blood pressure	Yes/Likely
11	Male	1979	IgA nephropathy	1.5 (6 mo), 2.25 (4 mo)	10	Proteinuria cleared, serum creatinine normalized	Yes/Likely
12	Male	2001	Enteric urolithiasis with acute renal failure	0.5 to 1.5	45	Elimination of kidney stones, normal serum creatinine maintained	Yes/Likely
13	Female	1960	Idiopathic chronic renal failure	1.5	3	Dramatic fall in proteinuria, serum creatinine stable	Yes/Likely
14	Male	2006	Congenital hydronephrosis with CKD	400 mg	1	No improvement, had kidney transplant	No
15	Female	1948	Status post nephrectomy for RCC stage I	1.5	1	No noticeable effect	No
16	Male	1943	Diabetic nephropathy, lupus nephritis	2.25	2	Slight increase in serum creatinine	No
17	Male	1949	Diabetic nephropathy	2	3	Progressive renal failure	No
18	Male	1974	Trauma resulting in kidney failure, status post transplant	1.5	1	Lost to follow-up	?
19	Female	1938	Hypertensive nephropathy	4.5	1	Lost to follow-up	?
20	Female	1973	MPGN	3	0.5	Lost to follow-up	?
21	Male	1928	Post-MI ischemic renal failure, diabetic nephropathy	1.5	2	Lost to follow-up	?

\*By searching electronic medical records, all patients with the keyword *Lespedeza* were located that were seen at Northwest Naturopathic Urology by Dr Yarnell from 2002 to 2010. All those who were actually prescribed *Lespedeza capitata* fresh herb tincture are recorded above. This was effective in many patients with a diversity of problems, always in conjunction with multiple dietary changes, dietary supplements, and medications (which differed between patients). Short-term (1 month or less) use of *lespedeza* tincture was rarely effective from these cases. IgA indicates immunoglobulin A; CKD, chronic kidney disease; MPGN, membranoproliferative glomerulonephritis; RCC, renal cell carcinoma; TURB, and transurethral resection of the bladder. Where a range of doses is given, the patient's herb formula was modified at some point.

models.<sup>26,27</sup>

At a dose of 1440 mg/d, a reishi extract was effective for lowering blood pressure in one preliminary Japanese clinical trial.<sup>28</sup> A different reishi extract at a dose of 55 mg 3 times per day was superior to placebo when added to ACE inhibitor

drugs in patients with hypertension not responding to drugs alone in one double-blinded trial.<sup>29</sup> These trials support that reishi has therapeutic effects on humans when administered by mouth, and appear to be ACE inhibitors. Additionally, reishi may be a nontoxic way to reduce hypertension, a well-

known cause of and aggravating factor for CKD.

Studies in patients with focal segmental glomerulosclerosis, a condition that frequently results in CKD, further highlights the importance of reishi for renal protection. Case series involving 19 adult Thai patients with focal segmental glomerulosclerosis (not responding to ACE inhibitor drugs, cyclophosphamide, and/or corticosteroids alone) have shown that reishi crude extract, 750 mg/d to 1100 mg/d, improved immunological balance and eliminated proteinuria in all subjects.<sup>30,31</sup>

*Salvia milthiorrhiza* (Chinese sage, *dan shen*) root is frequently utilized in traditional Asian medical systems for preventing and treating various forms of kidney disease. It is now becoming more widely known in the United States, as well. Chinese sage contains diterpenoids including tanshinones and caffeic acid derivatives such as danshensu and rosmarinic acid that impart ACE inhibiting, antioxidant, vasodilating, and blood thinning properties.<sup>32</sup>

No clinical trials in humans with CKD were located. However, it may be helpful in alleviating hypertension which can be beneficial in preventing renal disease. In one double-blind trial, a combination of extracts of Chinese sage, 450 mg, *Rhodiola rosea* (rose root) root, 40 mg, *Dendranthema x morifolium* (chrysanthemum) flower, 200 mg, and *Pueraria montana* (kudzu) root, 200 mg, twice daily was compared to placebo in Taiwanese adults for 12 weeks.<sup>33</sup> The herbal formula decreased systolic pressure and heart rate significantly compared to placebo in this trial with no difference in rates of minor adverse effects between groups.

According to one systematic review, existing evidence from multiple low-quality human trials shows that Chinese sage extracts can prevent onset of glomerulonephritis in patients with Henoch-Schonlein purpura.<sup>34</sup> One study in Chinese adults on chronic hemodialysis found that an injection of Chinese sage extract, 20 mg, with ligustrazine, 100 mg, once daily for 14 days lowered markers of platelet aggravation compared to untreated controls with no effect on kidney function.<sup>35</sup> An unknown extract of Chinese sage also lowered various markers of excessive oxidation and inflammation compared to untreated controls among Chinese adults undergoing chronic hemodialysis.<sup>36</sup>

Multiple preclinical studies suggest that various Chinese sage extracts can protect against or

mitigate various kidney diseases. This includes studies in rodents with diabetic nephropathy, doxorubicin-induced nephropathy, N(G)-nitro-D-arginine-induced oxidative nephropathy, 5/6 nephrectomy-induced CKD, and reperfusion injury after kidney transplant.<sup>37-42</sup> Much work remains to be done to work out the mechanisms and actions of Chinese sage extracts and compounds in vitro and in vivo.

Chinese sage can be used in multiple forms. A typical adult dose of tincture is 2 mL to 3 mL three times per day. A typical dose of granulation (spray-dried aqueous decoction) is 1g to 2 g three times per day. The typical dose of crude root is 3 g to 5 g per 250 mL of water decocted for 15 to 30 minutes, and 3 such portions are drunk per day. Chinese sage can enhance the effect of warfarin, leading to an increased risk of hemorrhage, and so the two should probably not be combined.<sup>43</sup> Whether or not Chinese sage interacts with platelet-inhibiting drugs has not been studied but caution is warranted before combining them.

## NEPHROPROTECTIVE HERBS

A number of herbal medicine used in the United States have documented abilities to protect nephrons against damage and destruction from a wide range of insults. Such herbs are therefore referred to as nephroprotectives (Table 1).

*Urtica dioica* (stinging nettle) seed has recently gained attention as a potential nephroprotective apparently originated with the herbalist David Winston from New Jersey. Naturopathic physicians and herbalists in particular appear to be those using it most often. The first published case studies supporting its benefits appeared in 2003 from the herbalist Jonathan Treasure, FNIMH of Ashland, Oregon.<sup>44</sup> In these cases, he used either a tincture of the fresh seeds alone, or a combination of this tincture with other herbs, in two patients with iatrogenic kidney damage. No further clinical publications have appeared since this time but empirical use of nettle seed continues.

In preclinical research, nettle seed has primarily been investigated for hepatic inflammation and disease. In rats challenged with aflatoxins, hepatotoxicity was almost completely abrogated by nettle seed compared to untreated rats.<sup>45</sup> Nettle seed oil, alone or in combination with seed oil of *Nigella sativa*, reduced hepatic and oxidative

damage due to carbon tetrachloride in rats.<sup>46</sup> In a rat model of ulcerative colitis, oral nettle seed oil reduced ulceration and multiple markers of inflammation compared to saline.<sup>47</sup>

*Silybum marianum* (milk thistle) seed contains a mixture of flavonolignans usually referred to as silymarin. This weedy Eurasian thistle is a promising nephroprotective, in part given its ecological sustainability. Though well known for its hepatoprotective effects, silymarin has similar though less well-researched protective effects on renal tissue. In animal studies, silymarin protected against renal damage due to a wide range of toxins and drugs including cisplatin, doxorubicin, cyclosporine, aminoglycosides, and paracetamol.<sup>48-51</sup> It mitigated ischemia/reperfusion damage to the kidneys.<sup>52</sup> Animal studies also support that silymarin reduces damage due to diabetic nephropathy as well as decreasing progression, in significant part thanks to enhanced function of the glutathione system.<sup>53,54</sup> Silymarin's various components, most notably silibinin and silicristin, stimulate regeneration of renal epithelium in vitro.<sup>55</sup>

Some human clinical trials give preliminary support to the use of silymarin or extracts of milk thistle seeds. In one clinical trial, 7 patients with CKD due to diabetic nephropathy were given a single intravenous infusion of silibinin 350 mg.<sup>56</sup> Baseline low glutathione levels improved over 72 hours, while T-cell activation in response to pokeweed mitogen improved and tumor necrosis factor-alpha release decreased.

Among fifteen patients on peritoneal dialysis for CKD who took silymarin 70 mg tid for 2 months, some had both a significant decrease in serum tumor necrosis factor-alpha levels and a simultaneous increase in hemoglobin levels compared to baseline.<sup>57</sup> In a double-blind trial, patients on hemodialysis for CKD were randomized to take silymarin 140 mg 3 times per day, vitamin E, 400 IU/d, a combination of both, or no additional treatment.<sup>58</sup> Erythrocyte glutathione peroxidase levels increased, serum malondialdehyde levels decreased, and hemoglobin levels increased significantly in the combination group compared to controls after 3 weeks.

Longer term and larger trials are warranted to determine the benefits of silymarin in patients with CKD including patients on dialysis. Silymarin is extremely safe. Standard oral doses are 140 mg

three times per day.

*Parietaria judaica* (pellitory-of-the-wall, pellitory), formerly known as *P diffusa*, is a member of the Urticaceae family native to Eurasia. The leaf and flower were historically used as urinary tract and kidney tonics.<sup>59</sup> This herb continues to be used empirically, at least among naturopathic physicians and herbalists, for this purpose in the United States, though very little research has been conducted on it. Its botanical relationship to *Urtica dioica* is interesting in this context, given the statements above about that plant. Pellitory has been shown to be diuretic.<sup>60</sup> The herb is extremely safe and a typical dose of a tincture is 3 mL to 5 mL 3 times per day.

*Rheum palmatum* (rhubarb) root comes from China and is now cultivated around the world. The cooked root, which decreases anthraquinone levels and thus reduces the cathartic nature of the plant,<sup>61</sup> has long been used as a kidney tonic in traditional Chinese medicine and is now also used frequently in the United States and other countries. Various preclinical models confirm that *R palmatum* reduces proteinuria, glomerulosclerosis, and excessive renal cellular proliferation.<sup>62,63</sup>

Several clinical trials have been conducted using rhubarb root extracts in patients with CKD. In one trial involving 38 patients, 1 g rhubarb per day maintained serum creatinine levels compared to rising levels seen in controls not treated with rhubarb.<sup>64</sup> In a group of 42 patients on hemodialysis, a *R palmatum* extract (dose undetermined) did not affect serum creatinine levels compared to no additional treatment, but it did improve lipid profiles.<sup>65</sup> In a study of 60 patients on hemodialysis, half were given a rhubarb extract (dose undetermined) along with Tongmai formula (ingredients not stated but includes *Pueraria lobata* [kudzu] and *Salvia miltiorrhiza* [dan shen]), for 1 month.<sup>66</sup> Dialysis efficacy, protein catabolic rate, and mean time urea nitrogen concentration were all better in those treated with the herbs compared to those on dialysis alone. In a group of 56 CKD patients, 36 were given a combination of rhubarb, *Panax ginseng* (Asian ginseng) root, *Astragalus membranaceus* (huang qi) root, *Cinnamomum cassia* (cassia) bark, and *Glycyrrhiza uralensis* (gan cao) root decoction (Baoyuan Dahuang) at an unspecified dose and 20 were given only standard conventional treatment, mainly coated aldehyde



oxystarch.<sup>67</sup> Symptoms improved significantly in the Baoyuan Dahuang group compared to controls. Serum creatinine fell to a similar degree in both groups (22% versus 29% respectively). Several of the other components of Baoyuan Dahuang will be discussed later in this article for their beneficial kidney properties.

These and many other trials support that rhubarb likely has a beneficial effect in patients with CKD, both to delay progression and to augment the efficacy while decreasing adverse effects of hemodialysis.<sup>68</sup> The ideal dose and timing is yet to be worked out, though in the US the most common ways are as a tincture of the cooked root, 1 mL, three times per day, or else as a granulation, 1 g to 2 g, three times per day. The dose should be lowered if catharsis occurs.

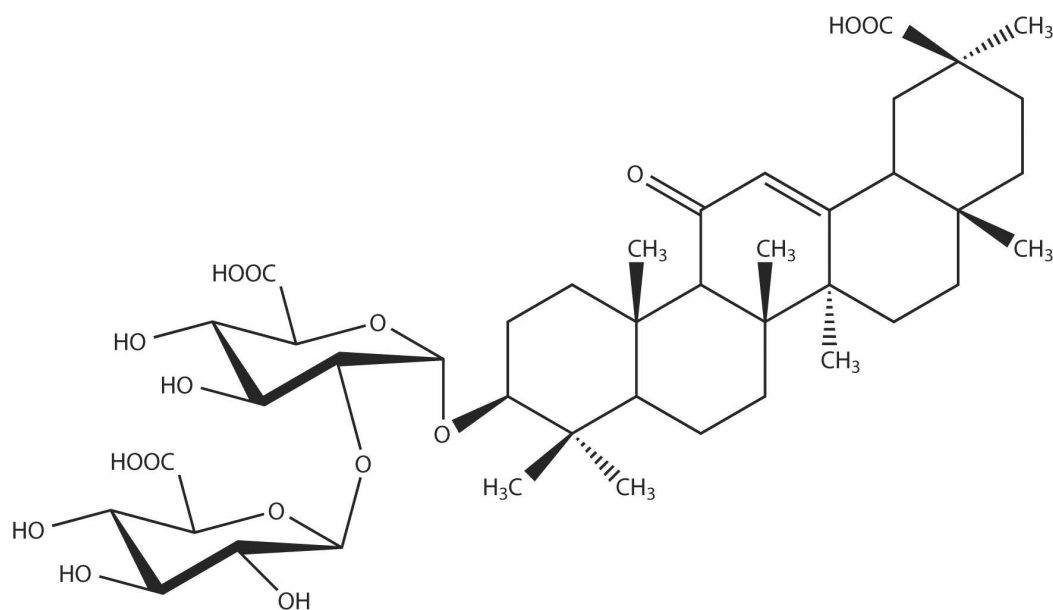
### IMMUNOMODULATING/ADAPTOGENIC HERBS

Another category of herbs with broad applicability to patients with CKD, whether or not they are on dialysis, are known as adaptogens or immunomodulators (Table 1). These herbs non-specifically improve resistant to stressors, such as a chronic disease like CKD, through multiple mechanisms in the nervous, endocrine, and immune systems.<sup>69</sup> Numerous reviews have been published on the various immunological activities, which are of interest to reduce autoimmune glomerulonephritis

in patients where this is the cause of their CKD and to counteract the immunosuppression common in CKD and particularly in dialysis patients.<sup>70,71</sup> Several adaptogenic immunomodulators that have been studied specifically in the setting of CKD will be discussed here.

*Glycyrrhiza glabra* (licorice) and *G uralensis* (gan cao) root are among the most widely used herbs in the world, including in the United States. *Glycyrrhiza glabra* is a shrub likely native to Central Asia but has been spread to temperate regions around the globe, while *G uralensis* is a shrub native to China and is also cultivated in many other areas. Both are sweet tasting due to the presence of the noncaloric triterpenoid glycoside glycyrrhizin, which yields glycyrrhetic acid and glucose upon hydrolysis (Figure). Extensive research on these molecules as well as other saponins and flavonoids in licorice and gan cao supports their historical use as immunomodulators and adaptogens, among many other uses.<sup>72-74</sup>

Many animal models looking at a range of insults to the kidneys have demonstrated that licorice or its various components, notably glycyrrhizin, have nephroprotective effects.<sup>75-79</sup> Licorice and gan cao may also treat various etiopathogenetic factors related to CKD. In a mouse model of glomerulonephritis, glabridin (a flavonoid from *G glabra*) was effective at reducing proteinuria through mechanisms unrelated to redox modulation.<sup>80</sup>



Glycyrrhizin

A prenylated isoflavone from *G uralensis* has been shown to inhibit mesangial sclerosis and inflammation related to diabetic nephropathy, as have the chalcone isoliquiritigenin and crude ethanolic and aqueous extracts of roasted gan cao root.<sup>81-83</sup> Decoctions of gan cao root have also been shown to improve clearance of immune complexes in rodent models, which might help in cases of CKD related to immune complex deposition.<sup>84</sup>

As noted in the discussion of rhubarb above, a combination formula known as Baoyuan Dahuang containing gan cao helped reduce symptoms in CKD patients better than standard care.<sup>67</sup> Glycyrrhizin has also been used to manage hyperkalemia in patients on hemodialysis in two trials. In the pilot double-blind crossover study, 7 anuric CKD patients were randomly assigned to glycyrrhizin 500 mg twice daily or placebo for 2 weeks, then after a 3-week washout period were crossed-over to the other treatment for 2 weeks.<sup>85</sup> Mean serum predialysis potassium fell from baseline of 5.5 mM/L to 4.5 mM/L after 2 weeks on glycyrrhizin, significantly more than placebo. There was no effect on blood pressure. In a follow-up double-blinded trial, 10 CKD patients on dialysis were randomly assigned to take cookies with glycyrrhizin 500 mg twice per day or without added glycyrrhizin.<sup>86</sup> Each treatment phase lasted 12 weeks. Predialysis serum potassium levels were above the upper limit of normal in 76% of patients during placebo phases and only 30% of those during glycyrrhizin phases, a significantly difference. Severe hyperkalemia occurred in only 0.6% of instances in patients during glycyrrhizin phases compared to 9% during placebo phases. No clear adverse effects of glycyrrhizin were noted with the possible exception of diarrhea in one patient. These data suggest that, with close monitoring of weight and blood pressure, CKD patients having difficulty with hyperkalemia may be able to be effectively treated with glycyrrhizin. Further research is warranted.

One report has stated that glycyrrhizin was used to safely and effectively to treat adenovirus infections in patients with renal transplants, suggesting it may be safe to combine with immunosuppressive drugs.<sup>87</sup> Licorice and glycyrrhizin have been shown to protect hepatocytes in vitro from the immunosuppressive drug azathioprine which is still sometimes used in renal transplantation or patients with glomerulonephritides.<sup>88</sup> Glycyrol, a

prenylated coumestan flavonoid found in licorice, has been shown to be a calcineurin inhibitor in rodents.<sup>89</sup> All this suggests the potential of a role of licorice even in patients on immunosuppressive drugs, though clearly more research is needed.

In overdose, *Glycyrrhiza spp* can ultimately lead to potassium deficiency sufficient to cause hypertension, rhabdomyolysis, acute renal failure, and death. Almost all such cases are due to patients overindulging in licorice candies or liqueurs and not use of medicinal preparations with medical supervision, and none have been reported in CKD patients.<sup>90</sup> Combination with thiazide diuretics enhances the likelihood of hypokalemic complications of licorice.<sup>91</sup> Monitoring of blood pressure and urine and/or serum potassium levels is recommended for any patient taking licorice for safety. Overall, licorice and compounds from this plant have strong potential to help patients in chronic renal failure.

*Cordyceps sinensis* (cordyceps) or *Ophiocordyceps sinensis*, known as dong chong xia cao (“winter worm, summer grass”) in Mandarin Chinese, is a traditional Tibetan and Chinese herb revered as a kidney tonic. It is now widely used in the United States as well. This fungus has one of the most unlikely life cycles of any medicinal substance: spores of the mature fruiting body are carried by water or wind and infect caterpillars and other insects, take over their bodies over the winter, and in the late spring or summer sprout out of the dead host as a visible sclerotium.<sup>92</sup> Due to its relatively narrow distribution on the Tibetan plateau and massive human overexploitation, it is now considered endangered in the wild.<sup>93</sup> For this reason, only cultivated mycelium of cordyceps should be used clinically, and such products have been shown to be an acceptable substitute for the whole wild sclerotium.<sup>94</sup>

Many clinical trials have been conducted using cordyceps in CKD patients. A benefit on immune function and kidney function in CKD patients was shown in one open study using 3 g to 5 g whole cordyceps for 10 to 12 months.<sup>95</sup> At least two studies on a cultivated mycelium extract at doses of 5 g to 6 g daily have been shown to improve kidney function, reduce anemia, and lower blood pressure in CKD patients.<sup>96,97</sup> There were no adverse effects associated with cordyceps treatment in these clinical trials.

Cordyceps has also been studied quite extensively as an adjunct therapy in patients who have undergone renal transplantation. In a one-year clinical trial, patients who underwent renal transplantation were all treated with cyclosporine, mycophenolate mofetil, and prednisone for chronic treatments after 5 days of methylprednisone and cyclophosphamide.<sup>98</sup> Half the group were randomly assigned to additionally take cordyceps mycelium extract 1 g three times daily. Twenty-four-hour urine protein levels, nephrotoxicity, hepatotoxicity, need for thymoglobulin antirejection treatment, chronic allograft nephropathy, and cyclosporine doses were significantly lower in the cordyceps group compared to the controls by the end of the trial. Similar results have been reported in prior smaller trials.<sup>99,100</sup>

Combining enalapril 10 mg daily and cordyceps mycelium extract 2 g twice a day was more effective than either alone or no additional treatment in a group of renal transplant patients with allograft nephropathy after 9 months.<sup>101</sup> Serum creatinine was significantly lower and creatinine clearance significantly higher in the combination group than groups treated with either agent alone or no additional treatment.

The root of *Codonopsis pilosula*, *C tangshen*, and *C lanceolata* (dang shen) is a Chinese herbal medicine that has been adopted into use in the United States, though there is far less clinical support for its use compared to cordyceps. It is immunomodulating and inflammation modulating.<sup>102,103</sup> It increases granulocyte macrophage colony-stimulating factor secretion by macrophages and thus may enhance hematopoiesis, including in the setting of CKD.<sup>104</sup> It also has experimental anti-diabetic activity, clearly important given how common diabetic nephropathy is as a cause of CKD.<sup>105</sup> Two different dang shen-containing formulas, only also containing cordyceps, have been tested in rat models of CKD and found to be somewhat helpful.<sup>106,107</sup>

*Astragalus membranaceus* root (called huang qi

in Chinese or astragalus in English) is a Fabaceae family shrub with a strong reputation for “[...] such problems as edema and proteinuria from chronic nephritis.<sup>108</sup>” Numerous animal studies confirm that it is immunomodulating and helpful for diabetic nephropathy.<sup>109,110</sup> Hematopoietic and thrombopoietic effects have also been demonstrated.<sup>111</sup> All these properties (Table 3) combined with its near total absence of adverse effects have made it popular in the United States for many conditions including CKD.

In one case study, a 77-year-old woman with idiopathic membranous nephropathy causing nephritic syndrome not responding to ACE inhibitors, angiotensin receptor blockers, or immunosuppressive drugs completely remitted when she took 15 g astragalus per day.<sup>116</sup> She relapsed when the herb was stopped and again remitted when she restarted treatment. There are few high-quality trials available, but three existing studies suggest that astragalus can increase plasma albumin, lower serum cholesterol, offset iatrogenic Cushing syndrome, and reduce respiratory tract infections rates in patients with nephritic syndrome.<sup>117</sup> There is very preliminary evidence of benefit of astragalus injection added to benazepril and dipyridamole therapy in patients with IgA nephropathy.<sup>118</sup> Numerous clinical trials support that astragalus is beneficial in patients with diabetic nephropathy for preventing progression as well as raising serum albumin levels.<sup>119</sup> Finally, astragalus has been shown safe and effective for improving immune function in patients on maintenance hemodialysis in a preliminary trial.<sup>120</sup>

Immunomodulating herbs, mainly originating from Chinese herbal medicine, have been avidly uptaken by North American practitioners of natural medicine for CKD patients. They are safe, effective, and offer actions not seen with other therapies.

## CONCLUSIONS

Numerous herbs are used in North America

**Table 3.** Additional Kidney Effects of *Astragalus* in Animals

Benefit	Model	Citation
Protection of renal tubules from lithotripsy	New Zealand white rabbits	Sheng et al <sup>112</sup>
Renal function protection against IgA nephropathy	Male Kunming albino mice	Huange et al <sup>113</sup>
Preventive against induction of glomerulonephritis by bovine serum albumin injection	Male Wistar rats	Liet et al <sup>114</sup>
Tubulointerstitial antifibrotic	Male Sprague-Dawley rats	Wojcikowski et al <sup>115</sup>



for patients with CKD. Some of these have been fairly well evaluated, though none optimally. Some herbs are used purely based on traditional use or extrapolation from animal studies without any clinical trials, a common practice in all forms of medicine. The risk of adverse effects appears to be low. Further research, either in clinical trials or real-world, whole-practice settings, is advocated. Many of these herbs have novel mechanisms of action that could yield enormous benefits.

### CONFLICT OF INTEREST

Dr Yarnell is part owner of Heron Botanicals, Inc, which produces extracts of some of the herbs discussed in this review.

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